REMARKS

In the outstanding Office action, claims 1 to 13 and 15 to 20 were presented for examination. Claims 11, 12, 15, and 17 stand withdrawn from further consideration. Claims 1-10, 13, 16 and 18-20 were rejected.

In this amendment applicant has amended each of claims 1, 4, 11, 16 and 17 and has added new claims 21-25. Thus, claims 1-10, 13, 16 and 18-25 are now pending for examination and claims 11, 12, 15, and 17 are believed eligible for rejoinder, as will be discussed in detail below. Accordingly, it is believed that the application is in condition for allowance.

Claim Amendments

Claims 1 and 16 have been amended, without narrowing, for better readability by introducing punctuation.

Claim 4 has been amended, without narrowing, to introduce the conjunction "and" between the molecular weight ranges cited.

Withdrawn product claims 11 and 17 have been amended for consistency with the method claims.

New claim 21 depends from claim 1 and recites that the reducing step comprises freeze drying in a particular manner as set forth in the claim. Support for new claim can be found at page 9, lines 15-16 of applicant's specification.

New claim 22 depends from claim 1 and recites that the maintaining step comprises sealing the vaccine composition in a particular manner as set forth in the claim. Support for new claim can be found at page 9, line 32 to page 10, line 3 of applicant's specification.

New claim 23 depends from claim 13 and recites that the lyophilizing step comprises reducing the water content of the vaccine composition to be below 2 weight percent.

New claim 24 depends from claim 13 and recites that the lyophilizing step comprises storing the dried vaccine composition and ensuring that the water content of the vaccine composition remains below 2 weight percent during storage. Support for new claim 24 can be found at page 8, lines 29-31 of applicant's specification.

New claim 25 depends from claim 13 and recites that the lyophilizing step comprises freezing the vaccine composition in the sol state. Support for new claim 25 can be found at page 9, lines 5-12 of applicant's specification, noting in particular, lines 10-12.

Rejoinder

The Office action states that the current status of rejoinder practice allows an applicant to rejoin the withdrawn process claims upon allowance of the elected product claims and references MPEP 821.04.

Applicant has carefully reviewed MPEP 821.04 and believes rejoinder of withdrawn product claims upon the allowance of elected process (method) claims is also proper pursuant to MPEP 821.04. In addition, product claims 11 and 17 have been amended for consistency with the method claims. Accordingly, rejoinder of product claims 11, 12, 15 and 17 at the appropriate time is respectfully requested.

Claim Rejections - 35 U.S.C. § 112 Second Paragraph

Applicant appreciates the withdrawal of the objection and rejection under 35 U.S.C. § 112 second paragraph, as was indicated in the outstanding Patent Office action.

Claim Objection

Claim 4 was objected to owing to a minor informality. The informality has been corrected by the addition of the word "and" to the claim, as was helpfully pointed out in the Office action. Accordingly, the objection is believed to have been overcome.

Claim Rejections - 35 U.S.C. § 102(b) Alleged Anticipation

In the outstanding Office action, claims 1-10, 13, 16 and 18-20 were stated to stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by International Publication No. WO 01/34801 ("the '801 publication" herein), "as evidenced by" U.S. Patent No. 6,685,940 ("the evidentiary reference '940 patent" herein) for the reasons set forth in the Office action mailed July 17, 2008.

In reply, applicant respectfully submits that applicant's claim 1, as now amended, is not anticipated by the '801 publication, but is patentably distinguishable from the '801 publication, for the reasons already of record and for new reasons which will now be explained. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Applicant's invention as claimed in claim 1 relates to a method for the preparation of a vaccine composition comprising recombinant or synthetic gelatin as a stabilizer. As recited in claim 1, the method comprises two steps. A first step comprises reducing the water content of the vaccine composition to be below 2 weight percent. A second step comprises maintaining the water content below 2 weight percent for at least 2 years. Though they may not be recited in claim 1, the method can comprise one or more additional steps, if desired.

On page 4, the Office action alleges that the two steps of applicant's process as recited in claim 1 are disclosed in the '801 publication because the referenced process

allegedly results in a "dry" formulation, as recited in the referenced claim 18. Applicant respectfully disagrees.

Applicant acknowledges that claim 18 of the '801 publication recites that the vaccine formulation of claim 1 of the reference is dry. However, applicant does not believe that the '801 publication discloses reducing the water content of the vaccine composition to be below 2 weight percent either explicitly or inherently. Applicant has found no explicit disclosure in the '801 publication of reducing the water content of the vaccine composition to be below 2 weight percent, as is recited in applicant's claim 1. and the Office action does not allege that such a disclosure exists.

Rather, the argument in the Office action for alleging anticipation of applicant's claim 1 rests on the meaning of the single word "dry". As applicant understands the Office action, the characterization of the vaccine formulation disclosed in the reference as dry is alleged to imply that a water below 2 weight percent is inherently disclosed in the '801 publication.

To support the argument, page 4 of the Office action references an edition of Webster's Dictionary and relies upon the definition there found to reach a conclusion as to the meaning of the word "dry" as the term is used in the '801 publication. The Office action states that the term "dry" is defined as "free from moisture or liquid, having all the water or liquid drained away, or evaporated" (emphasis added in the Office action). The Office action then concludes that because "all" liquid is removed by the process of reducing water (e.g. lyophilization) the referenced process meets the claimed limitation of reducing the water content of the vaccine composition to be below 2%" (emphasis also added in the Office action).

Applicant respectfully disagrees and submits that a person of ordinary skill in the art will form a different view of the '801 publication according to which the water

content of the vaccine formulation may not be below 2 percent by weight. Applicant's view is based, in part, upon evidence filed herewith regarding the knowledge of a person of ordinary skill in the art. In addition, applicant believes this view is consistent with an ordinary understanding of the word "dry".

In Applicant's view a person of ordinary skill in the art will have known that a freeze-dried biological material usually retains some water, "residual moisture" notwithstanding that the material has been dried. Support for this belief appears in the publication VICH Topic GL26 by the European Agency for Evaluation of Medicinal Products (2002) ("the VICH publication"). According to page 2, the VICH publication relates to the testing of residual moisture and is a guideline developed by an expert working group which is recommended for adoption by the regulatory bodies of the European Union, Japan and the USA.

Page 4 of the VICH publication states that

> Freeze-dried veterinary vaccines always contain some water, commonly known as residual moisture (RM). It is important to determine the level of RM in final products, since a satisfactory test gives assurance of an adequate shelf life...

The VICH publication further states that it is important to determine the residual moisture level in final products (for shelf life) and to confirm the residual moisture level is consistently within the manufacturer's specification. The document then provides guidelines for testing residual moisture referencing what is (not) specified by the U.S. Department of Agriculture and referencing the U.S. Code of Federal Regulations and describes test methods.

In light of the evidence provided by the VICH publication, applicant believes a person of ordinary skill in the art will expect that the freeze drying methods described

in the '801 publication will result in products that also contain some water, some "residual moisture".

Furthermore, the publication "The Determination of Residual Moisture in Dry Biological Substances" *J. Biological Chemistry* vol. 121, no. 1 (1937) to Flosdorf et al. shows that it has long been known in the art that dry biological materials can have a residual moisture content and that dryness is a question of degree.

As for the recitation in claim 18 of the '801 publication, that the vaccine formulation is "dry" one interpretation of the term "dry", in the context of claim 18, could be to distinguish the vaccine formulation there claimed from a liquid formulation, such as is claimed in claim 17 of the '801 publication. Here, definition 11 of the word "dry" in the dictionary cited in the Office action appears to be pertinent. Definition 11 reads as follows:

11. Of or pertaining to solid rather than liquid substances or commodities.

Clearly, the mere recitation in the '801 publication that the vaccine formulation is to be dry, without any further description being provided, does not necessarily mean that the described vaccine formulation must be "free from moisture" (i.e. entirely free of residual moisture). For example, the vaccine formulation could simply be dry rather than liquid. Or, the vaccine formulation could have, and in applicant's view probably does have, residual moisture as is described by the VICH publication.

In the absence from the '801 publication of any explicit disclosure of the water content of the vaccine formulation, Applicant believes that the '801 publication fails to discloses a method of reducing the water content of a vaccine composition to be below 2 weight percent, as is recited in applicant's claim 1.

The fact that a certain result or characteristic, for example a specific water content level, may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. See *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) and *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981).

To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted)

Applicant respectfully submits that the Office action does not allege that reducing the water content of a vaccine composition to be below 2 weight percent, as recited in applicant's claim 1, is explicitly disclosed in the '801 publication and has not shown that a water content below 2 weight percent is necessarily present in the dry vaccine formulation described in the '801 publication.

Applicant further respectfully submits, that the extrinsic evidence relied upon in the Office action, namely the definition of "dry" in Webster's II New Riverside University Dictionary, fails to make clear that the missing descriptive matter, namely reducing the water content of the vaccine composition to be below 2 weight percent, and maintaining the water content below 2 weight percent for at least 2 years, is necessarily present in the vaccine formulation described in the '801 publication. See

Continental Can Co. USA v. Monsanto Co.,948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

Accordingly, applicant believes claim 1 is not anticipated by the '801 publication but patentably distinguishable from the '801 publication, and is therefore allowable. Favorable reconsideration of the rejection and allowance of claim 1 are respectfully requested for this reason alone.

Furthermore, applicant believes the publication Journal of Immune Based Therapies and Vaccines 2007, **5**:4, entitled *Evaluation of a recombinant human gelatine as a substitute for a hydrolyzed porcine gelatine in a refrigerator-stable Oka/Merck live varicella vaccine* to Liska et al. ("Liska et al.") is relevant to what a person of ordinary skill in the art will recognize to be disclosed in the '801 publication.

Liska et al. was published in 2007, which is after the relevant date of applicant's claims, and is co-authored by two of the inventors of the '801 publication, namely Robert Chang and David Olsen.

Liska et al. describes the use of a 8.5 kD recombinant gelatine as a vaccine stabiliser in a lyophilized vaccine. On page 4, Liska et al. describes averaged moisture content values of vaccine samples containing respectively, hydrolyzed porcine gelatine and recombinant human gelatine prepared by freeze drying by a method which is described at page 3, lefthand column of the publication. As is described on page 4, following lyophilization, the samples were monitored during a long-term, 24-month, study under real-time conditions. During the study, the measured moisture content was 2.33% (+/- 0.12 standard error) for the porcine gelatine and 2.27% (+/- 0.07 std error) for the recombinant gelatine containing samples. As described in the publication,

no statistically significant trend in moisture content over time at 2-8° C was found for either formulation ($p > 0.05$) (page 4, top of the righthand column.)

Both of the measured moisture contents described in Liska et al. are significantly greater than the requirement recited in applicant's claim 1 that the water content of the vaccine composition is to be below 2 weight percent. Thus, Liska et al. describes a method of preparing a vaccine composition stabilized with a recombinant gelatin which has been lyophilized (or freeze dried), and which therefore can be understood to be "dry", can be prepared without meeting the requirements of applicant's claim 1.

Moreover, having regard to the authors-inventors which Liska et al. shares in common with the '801 publication, to the similarity of the technology described, and to the water content values described by Liska et al., applicant respectfully submits that neither the common authors-inventors, nor any other person of ordinary skill in the art would believe that the '801 publication disclosed reducing the water content of a recombinant-gelatin stabilized vaccine composition below 2 weight percent.

Furthermore the '801 publication is silent with regard to the problem of crystallization of recombinant gelatine. As is described in applicant's specification, at page 3, line 28 to page 4, line 1, vaccine formulations comprising recombinant gelatin stabilizer have a shorter shelf life compared to analogous compositions comprising animal-derived protein. Also, as described in applicant's specification, it was found that crystallization occurred in vaccine formulations employing a recombinant gelatin stabilizer during vaccine preparation and storage whereas such a problem had not been observed with animal-derived gelatin used in the art.

In applicant's view, the absence from Liska et al., which was co-authored by two of the inventors of the '801 publication, of any acknowledgment of the crystallization problem emphasizes that the teachings of the '801 publication lack an understanding of

the crystallization problem potentially associated with the use of recombinant gelatine as a vaccine stabilizer. Applicant believes this silence further clarifies that the '801 publication does not disclose the limitations recited in applicant's claim 1.

Accordingly, applicant respectfully submits that claim 1 is not anticipated by the '801 publication and is patentably distinguishable from the '801 publication, and therefore allowable, for this additional reason.

Applicant's claim 1 also recites maintaining the water content below 2 weight percent for at least 2 years and applicant believes that this limitation also is not disclosed in the '801 publication.

In relation to this limitation, the Office action argues, at the top of page 5, that "the referenced vial will inherently serve the intended use." Applicant understands "the referenced vial" to be the vial described in the evidentiary reference '940.

In reply, applicant respectfully points out that nothing in the evidentiary reference '940 appears to make clear that the missing descriptive matter, maintaining the water content below 2 weight percent for at least 2 years is necessarily present in method described in the '801 publication. As was explained above, inherency may not be established by probabilities or possibilities. See *In re Robertson*, supra.

Accordingly, applicant believes the '801 publication also does not anticipate applicant's claim 1 because the '801 publication, even when considered in the light of the evidentiary reference '940, does not disclose maintaining the water content below 2 weight percent for at least 2 years. Accordingly, claim 1 is believed to be still further patentably distinguishable from the '801 publication, and therefore allowable, for this additional reason.

In light of the above explanation of the reasons given for patentability, reconsideration and allowance of claim 1 are respectfully requested.

In the outstanding Office action, claims 1-10, 13, 16 and 18-20 were also again rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by US 2003/0064074 ("the '074 publication" herein), as evidenced by U.S. Patent No. 6,685,940 for the reasons set forth in the Office action mailed (prepared?) 7/17/08.

As was explained in the last Amendment, applicant believes that the disclosure of the '074 publication is similar to that of the '801 publication. The '074 publication does not appear to add anything to the grounds for rejection appearing elsewhere in the outstanding Office action. Accordingly, applicant believes that amended claim 1 is patentably distinguished from the '074 publication, and therefore allowable, for the same reasons that amended claim 1 is believed to be patentably distinguished from the '801 publication.

Claim 13 relates to a method for the preparation of a vaccine composition comprising recombinant or synthetic gelatin as a stabilizer and recites, inter alia, lyophilizing a vaccine composition with sufficient drying to prevent crystallization of a recombinant gelatin during the lifetime of the vaccine composition

As is explained herein, neither the '801 publication nor the '074 publication describes the problem of crystallization of recombinant gelatin in a vaccine composition. Furthermore, neither the '801 publication nor the '074 publication discloses lyophilizing a recombinant gelatin containing vaccine composition for sufficient time to prevent crystallization of the recombinant gelatin.

Accordingly, applicant respectfully submits that Claim 13 is also patentably distinguishable from either the '801 publication or the '074 publication, and is therefore

allowable. Favorable reconsideration and allowance of claim 13 are respectfully requested.

Claim 16 contains limitations similar to amended claim 1 and applicant respectfully submits that claim 16 is also patentably distinguishable from the '801 publication or the '074 publication, for the same reasons as claim 1 is believed to be patentably distinguishable from these references.

Dependent Claims

Claims 2-10 and 18-20 depend either directly or indirectly from amended claim 1, incorporate all the limitations of claim 1 and therefore are believed allowable for at least the same reasons that amended claim 1 is believed allowable. Applicant believes that dependent claims 2-10 and 18-20 also are patentably distinguishable from the art of record, and therefore allowable, by the additional limitations they recite.

Apparently in relation to claim 8, the Office action states that "Applicant's assertion that the referenced lyophilized vaccine is not stable for 24 months of storage and the citation of p. 60 as a basis for the assertions is misleading."

Applicant has carefully reviewed the relevant text in the Amendment filed November 24, 2008 ("the last Amendment") and respectfully submits that no misleading assertion was made.

In the last Amendment filed November 24, 2008, applicant explained that Claim 8 specifically recites that the water content is maintained below 2 weight percent to prevent crystallization of the recombinant or synthetic gelatin for at least 7 years, which is not remotely suggested by the '801 publication or any of the other art of record in this application. Applicant supported this latter argument with a quotation from the '801 publication. The relevant text in the last Amendment reads as follows:

> The Office action refers to the disclosure on page 60 of the '801 publication, and alleges that the '801 publication further teaches that the lyophilized vaccine is stable for 24 months of storage. Applicant respectfully submits this statement is an incorrect characterization of the reference. The '801 publication actually states, at page 60, lines 36-37 that
>
> > Lyophilized vaccines slowly deteriorate until, at around 12 to 24 months of storage, the vaccine formulation lacks sufficient titer to confer immunization.
>
> Accordingly, applicant believes the '801 publication also does not disclose the additional subject matter recited in claim 8.

As can be seen, in this statement there is no assertion by applicant that the referenced lyophilized vaccine is not stable for 24 months. There is merely a statement of applicant's belief that the '801 publication also does not disclose the additional subject matter recited in claim 8. Accordingly, the Office is respectfully requested to reconsider and withdraw the allegation that applicant made a misleading assertion.

The above-quoted passage from the last amendment relates to an allegation on page 4 of the Office action mailed July 22, 2008 that the '801 publication teaches that the lyophilized vaccine is stable for 24 months of storage, citing page 60 of the reference. Applicant made the above-quoted statements to rebut this allegation because applicant was unable to find on page 60 of the reference any support for the proposition in the Office action that the referenced lyophilized vaccine is stable for 24 months of storage. Furthermore, nothing appears to be added in the final Office action to change this view.

Applicant once again respectfully submits that claim 8 is additionally patentably distinguished from the '801 publication by the subject matter recited in claim 8, namely that the water content is maintained below 2 weight percent to prevent crystallization of the recombinant or synthetic gelatin for at least 7 years. Nothing in the '801 publication or any of the other art of record appears to disclose or suggest this subject matter. Favorable reconsideration and allowance of claim 8 are respectfully requested.

New claims 21-25 recite limitations which applicant believes are not found in either the '801 publication or the '074 publication. Accordingly, applicant respectfully submits that each of new claims 21-25 is additionally patentably distinguishable from the art of record by the limitations each claim recites.

For example, new claim 21 recites that freeze drying the vaccine composition and keeping the temperature below a calculated glass transition temperature of the vaccine composition during freeze drying.

Also, new claim 22 recites sealing the vaccine composition in an air- and moisture-tight container under an oxygen-free gas or under vacuum.

And, new claim 25 recites that the lyophilizing step comprises freezing the vaccine composition in the sol state.

Conclusion

In view of the above amendments and the discussion relating thereto, it is respectfully submitted that the instant application, as amended, is in condition for allowance. Favorable reconsideration and allowance are earnestly solicited. If for any reason the Examiner feels that consultation with applicant's representative would be helpful in the advancement of the prosecution, the Examiner is invited to contact the undersigned practitioner.

Respectfully submitted,

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